REMARKS

Status of Claims and Request for Rejoinder of Method Claims

Claims 1-114 were pending in the present application. Claims 42-114 were withdrawn from consideration. By virtue of this response, claims 8, 11-17, 59, 61-67, 87, and 114 have been cancelled and claims 1, 9, 22, 27, 42, 56, 58, 60, 68-73, 76, 88, 89, 102, 104, and 106-111 have been amended.

Amendment of claims 9, 60, and 88 reflects an update of claim dependency due to the cancellation of claims 8, 59, and 87, respectively, and, as such, does not constitute new matter. Amendment of claim 22 corrects an obvious typographical error and, as such, does not constitute new matter. Support for the amendment of the remaining claims can be found throughout the specification and claims, as originally filed, and, in particular on page 7, lines 30-23; page 8, lines 4-9 and lines 25-28; page 16, lines 5-16; page 18, lines 9-19; page 23, line 22 through page 24, line 8; and Example 1. No new matter is believed to have been added.

With respect to claim amendments and cancellation, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

The Applicants note that the Examiner recognized, in the Office Action dated June 8, 2004 and requiring restriction of the originally pending claims (Paper No. 9), that groups I and II are linked by claim 1. The Examiner further stated that upon indication of allowable subject matter of the claim 1, the restriction requirement as to groups I and II would be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the present application.

Applicants therefore respectfully request rejoinder of the withdrawn method claims 42-58, 60, 68-86, and 88-113 (directed to methods of using the claimed complexes) upon allowance of the elected product claims, in accordance with MPEP §821.04 ("Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. . . . However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined."). Independent method claims 42, 76, and 89, and therefore their dependent claims 43-58, 60, 68-75, 77-86, 88, and 90-113, have been amended to incorporate all of the limitations of product claim 1. Applicants therefore respectfully request rejoinder of these method claims upon allowance of the product claim whose limitations they incorporate and further request that these method claims be examined for patentability in accordance with 37 C.F.R. §1.104 upon allowance of the product claims.

The Applicants further note that currently withdrawn claims 56, 58, 68-73, 102, 104 and 106-111 have been amended in order to further prosecution and to reflect amendment of similarly-phrased claims 7, 18-26, 30, 31, and 33-41 in the response to the previous Office Action filed with the Office on March 17, 2005. As previously noted, such amendment does not indicate that the Applicants acquiesce to the Examiner's statements regarding claims 7, 18-26, 30, 31, and 33-41 in the previous Office Action nor does the present amendment indicate that the Applicants believe similar remarks would be warranted with respect to claims 56, 58, 68-73, 102, 104 and 106-111 and therefore the amendment is presented solely to avoid further delay in prosecution of the present application.

Regarding the Supplemental Information Disclosure Statement (SIDS)

The Applicants thanks the Examiner for review of the previously-submitted references and return of the initialed PTO SB/08 and PTO-1449 forms. The Applicants note for the Examiner's convenience that a Supplemental Information Disclosure Statement is filed herewith. The Applicants respectfully request review of the submitted references and return of the initialed PTO SB/08.

The Applicants note that the present SIDS contains two references, including the reference originally submitted as no. 78 (IDS filed May 9, 2002) (Weiss *et al.,* (1987) *Bull. Hosp. Jt. Dis. Orthop. Inst.* **47**:31-39), which the Examiner indicated he did not receive with the originally-filed IDS. The Applicants note that the return receipt postcard indicated receipt of all references by the Office. In order to further the prosecution of the present application, should either of the references cited in the present SIDS not be received by the Examiner, the Examiner is earnestly entreated to contact the undersigned at his earliest convenience so that a duplicate copy of any missing reference may be provided without delay and so that the Examiner may consider the references prior to the issuance of a further action.

Regarding the Interview Summary

The Applicants thank the Examiner for his time and the interview granted on October 5, 2005. The Applicants also acknowledge receipt of the facsimile copy of the interview summary received on October 5, 2005. For the record the Applicants note that the interview summary contains a typographical error as indicated below.

The interview summary states that "Applicant's Representative indicates that the secondary references do not teach a composition of an aqueous dispersion of **soluble** non-crosslinked type I fibrillar atelopeptide collagen …." However, in fact, Applicant's representative asserted that the secondary claims do not teach a composition of an aqueous dispersion of **insoluble** non-crosslinked type I fibrillar atelopeptide collagen, consistent with the claims.

The Applicants note that in a follow up telephone conversation with the undersigned on October 5, 2005 the Examiner confirmed that the interview summary should recite "insoluble" and not "soluble" non-crosslinked type I fibrillar atelopeptide collagen and that the use of the term "soluble" was a typographical error.

Objections to the Abstract and Use of Trademarks and Rejections under 35 U.S.C. §112, 2nd ¶

The Applicants thank the Examiner for the withdrawal of the objections to the Abstract and specification and the withdrawal of the rejections under 35 U.S.C. §112, 2nd ¶.

Objection to Claim 1

Claim 1 is objected to for not being limited to the elected species (*i.e.*, anesthetics) and subspecies A (bupivacaine).

At the suggestion of the Examiner and in order to further prosecution of the present application, claim 1 has been amended to recited only the elected species (anesthetics). By amendment of claim 1 the Applicants do not acquiesce to the Examiner's statement that the elected species is unpatentable (paper no. 9, page 2, ¶2).

Applicants assert that such amendment does not constitute new matter and, in view of the amendment, request withdrawal of the objection to claim 1.

Rejections under 35 U.S.C. 103

Claims 1-10 and 18-41 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Pavelka et al., Poster No. 137 of "Safety Following Intra-articular Injection of Neu Visc™--Two Studies". The Applicants respectfully traverse the rejection.

The Applicants note that cancellation of claim 8 renders the above-listed rejection moot with respect to this claim.

As noted previously, and as acknowledged by the Examiner in the Office Action (paper no. 9), page 6, Pavelka et al. does not teach or suggest the ratio of collagen to pharmaceutical agent recited in independent claim 1, and therefore its dependent claims 2-10 and 18-26, and likewise does not teach the ratio of collagen to bupivacaine in independent claim 27 and therefore its dependent claims 28-41. The Examiner also acknowledges on page 6 of the Office Action that Pavelka does not teach the duration time of controlled release, the amount or percentages of type I collagen, the concentration of the collagen or the pharmaceutical agent or the use of bupivacaine. Thus, Pavelka does not teach nor suggest the limitations of the claimed invention as a whole. As noted in the present specification at page 20, lines 3-6, the amount of lidocaine present in the Pavelka compositions will result in an effective anesthetic effect for less than an hour, usually only a few minutes.

With regard to the secondary references, the Applicants note that Solanki *et al.*, describes the use of bupivacaine for intraarticular injection but does not teach or suggest the use of bupivacaine in combination with insoluble non-crosslinked type I fibrillar atelopeptide collagen. Indeed, Solanki *et al.*, makes no mention of the combination of bupivacaine with any type of collagen and certainly does not suggest a collagen to pharmaceutical agent or collagen to bupivacaine ratio as recited in independent claims 1 and 27 and therefore their dependent claims. Thus, the teachings of Solanki *et al.*, would not suggest to one of skill in the art the modification of the composition described in Pavelka to achieve a ratio of collagen to pharmaceutical ratio or bupivacaine as recited in the independent claims and therefore in the dependent claims.

As is well known to those of skill in the art and described in the specification (*e.g.*, pages 4, 13-14,) there are a number of different types of collagens (*e.g.*, fibrillar, non-fibrillar, type I, type III, atelopeptide, etc.) and the properties of these collagens differ, both with respect to physical characterization (*e.g.*, solubility, macromolecular structure, etc.) and with regard to what could be termed pharmokinetic properties (*e.g.*, the ability to retard the release of pharmaceutical agents, drug release profiles, etc.). Additionally, the preparation of the collagen (*e.g.*, film, matrix, pellet, etc.) of the particular collagen is also known to effect the drug release profile. Thus, one of ordinary skill would not expect the drug release profile of, for example, an aqueous dispersion of insoluble

non-crosslinked type I fibrillar atelopeptide collagen and non-fibrillar collagen to be the same. (*See e.g.,* Wallace *et al., Advanced Drug Delivery Reviews* (2003) **55**: 1631-1649.) Indeed, the accepted wisdom in the field before (and after) the priority date of the present application was that fibrillar collagen was not effective in moderating the release rates of small molecules, such as the anesthetics presently claimed, unless the collagen was treated either chemically (*e.g.,* crosslinking) or mechanically (*e.g.,* extruded in particular ways or formed into matrices of particular types).

For example, prior to the priority date of the present application, it was generally believed in the field that in order to observe moderated release rates for drugs/active ingredients from fibrillar collagen the formulation must be treated in some manner to chemically bind the active and the collagen or the active must be large enough for its diffusion from the collagen matrix to be hindered or the collagen somehow mechanically processed to hinder release. For example, Rosenblatt *et al.,* (*J. Controlled Release* (1989) **9**: 195-203) state that "Fibrillar collagen matrices were capable of moderating the release rates of very large proteins only (such as fibrinogen) and a *significant non-fibrillar content was necessary* to modulate the diffusivity of smaller proteins such as chymotrypsinogen" (Abstract, emphasis added) and "In order to control the release of small proteins by hindering the diffusion rates, the matrix must contain a significant concentration of non-fibrillar or microfibrillar collagen " (pg. 203 "Conclusions"). Typical anesthetics and/or analgesics are far smaller than even the small proteins discussed by Rosenblatt et al., (for example, bupivacaine has a molecular weight of 325 (http://ramanathans.com/localchapterram[1].htm)), and there would be no expectation by those of skill in the art that the modulated release of the proteins described by Rosenblatt would be observed for small molecules of this size.

After the filing date of the present application the accepted view by those of skill was still that small molecules would not experience hindered diffusion (modulated release rates) from fibrillar collagen suspensions, as noted by Wallace et al., in a review of the field of collagen suspensions in 2003. *See e.g.,* Wallace, *ibid*, Section 3.2, pg. 1638, col. 2: "Release of small molecules": "Based on the reasoning about collagen structure, drug molecules (mol. wt. 0.5 to 2 kDa, molecular dimensions 9.5 to 1.5 nm) should not experience hindered diffusion in transport through FCS (mesh size estimate: 58 nm). . ." (where "FCS" is fibrillar collagen suspension) and

"Diffusion-dominated release of dissolved small molecules from collagen gels may be predicted to resemble that in Fig. 3 … [ref 38]. The drug was 80% depleted in only about 8 min." To overcome this rapid diffusion-controlled release for small molecules, scientists in the field would expect it to be necessary to somehow bind the drug to the collagen, otherwise treat the formulation to hinder the release rate (*e.g.,* cross-linking), or incorporate additional components such as non-fibrillar collagen.

The remaining secondary references cited, Yamahira et al., Maeda et al., and Baytrov et al., do discuss the uses of collagen, but these secondary references neither teach nor suggest the use of the specific collagen as recited in the claims, nor do they suggest preparations that are aqueous dispersions of the particular collagen recited in the claims. In other words, the secondary references would not be considered relevant to those of ordinary skill working with an aqueous dispersion of insoluble non-crosslinked type I fibrillar atelopeptide collagen as recited in the claims.

While Yamahira et al., refer to "atelocollagen" there is no suggestion that this atelocollagen is insoluble non-crosslinked fibrillar atelopeptide collagen. In fact, Yamahira et al., consistently characterize their formulations, prior to drying, as solutions of collagen and active ingredient (*e.g.,* "For instance, an aqueous collagen solution contains usually a buffer…" col. 3, lines 8-9; "An active ingredient or an aqueous solution thereof is mixed with a biodegradable carrier or aqueous solution thereof …" col. 3, lines 31-33). As known to those of ordinary skill, a "solution" requires that the solute (in this case active and collagen) be dissolved in the solvent (water). Solutions and dispersions (suspensions of insoluble component(s)) are recognized to be different by persons of ordinary skill. Thus, the atelocollagen that Yamahira et al., are using is soluble atelocollagen, and therefore cannot be the same type of collagen as recited in the present claims, which require as a limitation that it be "insoluble" and fibrillar. As is known to those of ordinary skill, fibrillar peptide is not soluble. The Examples in Yamahira also support the conclusion that Yamahira pertains to a different type of collagen in that the Examples describing the preparation of the collagen compositions refer to *dissolving* the atelocollagen in distilled water, along with the active ingredient. (Examples 1-3, 7, and 11). For example, "An aqueous solution of α-interferon … and atelocollagen powder (1g) are mixed, and the resulting solution is entered into a

mold and lyophilized." (Example 11, Col. 6).

As noted, above, the characteristics of the various types of collagens are different and their properties with regard to drug release are also recognized to be different, thus disclosure pertaining to the drug release properties of soluble atelocollagen as used in Yamahira would not be considered relevant by one of ordinary skill to preparations such as those disclosed in Pavelka et al., and therefore one of skill would not be motivated to modify the compositions disclosed in Pavelka based on the disclosure of Yamahira et al. Thus, the Applicants assert that the claims as presently presented are not obvious in view of the cited references, either alone, or in combination.

Similar to Yamahira et al., Maeda et al., do not describe the use of aqueous dispersions of insoluble non-crosslinked type I fibrillar atelopeptide collagen. Like Yamahira et al., Maeda et al., disclose the use of atelocollagen and also refer to their collagen being in solution ("Aqueous solutions of HSA and collagen were mixed, and the mixture freeze dried" (page 315, col. 1, section 2.3.1); "Aqueous solutions of HSA and collagen were mixed and poured into petri-dishes …" (page 315, col. 1, section 2.3.2)).

For the record, the Applicants also note that Maeda et al., also attribute the delayed release achieved by using their soluble non-crosslinked collagen to the manufacture process, which requires extrusion, as their other formulations did not exhibit delayed release of the active ingredient ("Though the collagen in the minipellet was not cross-linked, the dense structure of collagen matrix during the release was maintained by the manufacturing method." (pg. 318, col. 1)).

Therefore, as reasoned above with regard to Yamahira, the collagen used by Maeda can be neither insoluble nor fibrillar as required by the present claims and one of ordinary skill would not be motivated to apply the disclosure of Maeda *et al.,* to modify the compositions described in Pavelka et al. and thus the cited references, alone or in combination, neither teach nor suggest the claims as presently presented.

As in Yamahira et al., and Maeda et al., Baytrov et al. (see translation co-filed herewith in the accompanying SIDS) refer to their collagen compositions as solutions. For example, "1, 2, 3,

and 4% solutions of trimecaine, ... in aqueous collagen solution ..." (pg. 2, lines 8-9); "3- 1% solution of tremecaine-collagen complex;" (pg. 6, Fig. 2 legend); "Further, one can presume the existence of a tendency for increase in the depth of anesthesia when using collagen-containing solutions of treimecaine as compared to aqueous solutions, ..." (pg. 6, lines 22-26). That these solutions do not use the same type of collagen as the present claims is also evidenced by the fact that the collagen-trimecaine solutions of Baytrov et al., only prolong pain relief for less than an hour, while the examples of the claimed compositions show controlled release of the anesthetic over a period of, for example, 60-72 hours (see example 1 of the present application).

Thus, as reasoned above with regard to Yamahira et al., and Maeda et al., the collagen used by Maeda can be neither insoluble nor fibrillar as required by the present claims and one of ordinary skill would not be motivated to apply the disclosure of Baytrov *et al.,* to modify the compositions described in Pavelka et al. and thus the cited references, alone or in combination, do not teach or suggest the claims as presently presented.

In conclusion, the Applicants assert that the claims as presently presented are not obvious over the cited references and, further, that Wallace et al., *ibid* and Rosenblatt et al., *ibid*, discussed above and as examples of the accepted wisdom of the field support this assertion (MPEP 2145 X, D3 "Proceeding Contrary to Accepted Wisdom is Evidence of Nonobviousness"). With regard to Pavelka et al., Solanki et al., Yamahira et al., Maeda et al., and Baytrov et al., the Applicants assert, for the reasons presented above, that the claimed invention as a whole is not obvious in view of the cited references and that one of ordinary skill in the art would not be motivated to modify the compositions described in Pavelka et al., to prepare an aqueous dispersion of insoluble non-crosslinked fibrillar atelopeptide collagen with a ratio of collagen to pharmaceutical either of 0.5:1 to 10: 1, either based on Pavelka alone or in combination with any or all of the secondary references cited by the Examiner.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is earnestly entreated to telephone the undersigned at the number given below prior to the issuance of a further action in the present application.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **437252001200**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By _____

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